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PATENT SPECIFICATION (11) 1390772

(21) Application No. 11319/72 (22) Filed 10 March 1972
(31) Convention Application No. 141407 (32) Filed 7 May 1971 in
(33) United States of America (US)
(44) Complete Specification published 16 April 1975
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(19)

(54) ORAL NARCOTIC COMPOSITION

(71) We, ENDO LABORATORIES INC., a Corporation organised and existing under the Laws of the State of Delaware, located at 1000 Stewart Avenue, Garden City, New York 11530, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to an oral narcotic capsule or syrup, comprising a narcotic which has substantial activity orally as well as by injection, in combination with a narcotic antagonist which is much less effective orally than by injection, the ratio of antagonist to narcotic in the combination being such that the antagonist does not block the effect of the narcotic when the combination is administered orally, but does prevent the obtainment of an acute euphoriant effect when the combination is administered by injection.

When administered orally in unit dosage form, the composition provides a fully effective therapeutic dose of the narcotic, substantially undiminished by presence of the antagonist. However, when the combination of active ingredients is extracted and injected, the antagonist effectively blocks the effect of the narcotic, preventing obtainment of the desired euphoriant effect. Thus, the combination removes the incentive for diversion of the drugs into other channels and uses.

The narcotic drug which can be used in the compositions of this invention is oxycodone, hydrocodone, codeine, propoxyphene or pentazocine or a pharmaceutically acceptable salt thereof. Propoxyphene is not at present under narcotic control, but it is definitely recognised as a weak narcotic, and has been incriminated

PATENTS ACT 1949

SPECIFICATION NO 1390772

Amendment is made in accordance with the Decision of the Principal Examiner acting for the Comptroller-General, dated the 3rd day of October 1977 under Section 9 in the following manner:-

Reference has been directed in pursuance of Section 9 subsection (1) of the Patents Act 1949 to Patent No 1353815.

THE PATENT OFFICE
10 November 1977

Bas 42365/3

vention is one suitable for oral administration and comprising (a) a compound having substantial narcotic activity both orally and by injection, the compound being oxycodone, hydrocodone, codeine, propoxyphene or pentazocine or a pharmaceutically acceptable salt thereof, and (b) a narcotic antagonist which is substantially less active orally than by injection, the narcotic antagonist being (1) naloxone or a pharmaceutically acceptable salt thereof, (2) N - cyclopropylmethyl - 7,8-dihydro - 14 - hydroxynormorphinone or a pharmaceutically acceptable salt thereof, or (3) 21 - cyclopropyl - 7β - (1 - hydroxy - 1-methylethyl) - 6,14 - *endo* - ethanotetrahydrooripavine or a pharmaceutically acceptable salt thereof, the weight ratio of (a) to (b), calculated as the free base, being

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This invention relates to an oral narcotic composition.

In general, narcotic addicts do not obtain narcotic satisfaction or a "high" from the comparatively slow, diffuse, and attenuated effect of narcotics taken orally. Instead they seek the rapid, concentrated, and undiminished effect of an injected narcotic, preferably intravenous or "mainline", to achieve the desired acute euphoriant effect of a satisfactory "high". Consequently, addicts sometimes obtain the more easily procurable oral narcotics such as analgesics and antitussives, and extract the narcotic substance so that it can be injected. Thus, narcotic abuse through diversion of oral narcotic therapeutic drugs into channels for injection by addicts has become a serious problem in medicine and public health.

This invention provides a narcotic composition for oral administration, e.g. a tablet, capsule or syrup, comprising a narcotic which has substantial activity orally as well as by injection, in combination with a narcotic antagonist which is much less effective orally than by injection, the ratio of antagonist to narcotic in the combination being such that the antagonist does not block the effect of the narcotic when the combination is administered orally, but does prevent the obtainment of an acute euphoriant effect when the combination is administered by injection.

When administered orally in unit dosage form, the composition provides a fully effective therapeutic dose of the narcotic, substantially undiminished by presence of the antagonist. However, when the combination of active ingredients is extracted and injected, the antagonist effectively blocks the effect of the narcotic, preventing obtainment of the desired euphoriant effect. Thus, the combination removes the incentive for diversion of the drugs into other channels and uses.

The narcotic drug which can be used in the compositions of this invention is oxycodone, hydrocodone, codeine, propoxyphene or pentazocine or a pharmaceutically acceptable salt thereof. Propoxyphene is not at present under narcotic control, but it is definitely recognised as a weak narcotic, and has been incriminated in some cases of narcotic drug abuse and addiction. Pentazocine likewise is not at present under narcotic control in the U.S.A.; however, it is a mixed weak narcotic antagonist and borderline narcotic, from which the narcotic component has emerged sufficiently to cause a significant number of cases of drug abuse and addiction.

The narcotic antagonist used in the invention has substantially greater effectiveness when administered by injection than when administered orally; the antagonist is naloxone, N - cyclo propylmethyl - 7,8 - dihydro - 14-hydroxynormorphinone or 21 - cyclopropyl-7α - (1 - hydroxy - 1 - methylethyl) - 6,14-*endo* - ethano - tetrahydrooripavine (or diphenorphine) or a pharmaceutically acceptable acid addition salt thereof.

The pharmaceutical composition of the invention is one suitable for oral administration and comprising (a) a compound having substantial narcotic activity both orally and by injection, the compound being oxycodone, hydrocodone, codeine, propoxyphene or pentazocine or a pharmaceutically acceptable salt thereof, and (b) a narcotic antagonist which is substantially less active orally than by injection, the narcotic antagonist being (1) naloxone or a pharmaceutically acceptable salt thereof, (2) N - cyclopropylmethyl - 7,8-dihydro - 14 - hydroxynormorphinone or a pharmaceutically acceptable salt thereof, or (3) 21 - cyclopropyl - 7β - (1 - hydroxy - 1-methylethyl) - 6,14 - *endo* - ethanotetrahydrooripavine or a pharmaceutically acceptable salt thereof, the weight ratio of (a) to (b), calculated as the free base, being

a	Ratio with (b) (1)	Ratio with (b) (2) or (3)
oxycodone	5:0.1	15:0.1
hydrocodone	5:0.03	5:0.01
codeine	30:0.1	90:0.1
propoxyphene	65:0.2	195:0.2
pentazocine	50:0.2	150:0.2

so that (b) does not block the narcotic effect of (a) when the composition is administered orally but does prevent an acute euphoriant effect by (a) when the composition is injected.

The compositions of the invention are conventional oral narcotic compositions, except for the inclusion of the narcotic antagonist. In the case of tablets, they will generally contain 5—100 mg of the narcotic and 0.001—50 mg (usually 0.003—5 mg) of the antagonist. Liquid preparations will generally contain 1—20 mg/ml of the narcotic and 0.0002—10 mg/ml (usually 0.0006—1 mg/ml) of the antagonist. Additional drugs, e.g. antihistamines, non-narcotic analgesics and antispasmodics may be included, along with conventional excipients in conventional amounts.

The following are some specific Examples of the compositions of the invention and the uses to which they can be put.

Example 1.

Oxycodone with Naloxone — Oxycodone is an effective oral narcotic analgesic and is generally used in a dose of about 5 mg. of oxycodone hydrochloride per tablet, together with aspirin, phenacetin and caffeine (similar to the well known "APC with Codeine"). The addict would probably have to inject the narcotic extract from 6—12 tablets to obtain a "high".

In the compositions of this invention, the tablet (or 5 ml dose of liquid) should contain about 5 mg of oxycodone hydrochloride (or equivalent as the base or salt) together with 0.01—0.3 mg. of naloxone hydrochloride (or equivalent as base or salts) with or without additional drugs such as aspirin, phenacetin and caffeine. The preferred tablet dose is oxycodone hydrochloride 5 mg. and naloxone hydrochloride 0.1 mg., together with aspirin 224 mg., phenacetin 160 mg., and caffeine 32 mg.

Example 2.

Hydrocodone with Naloxone — Hydrocodone is an effective oral narcotic antitussive-analgesic and is generally used in a dose of about 5 mg. of hydrocodone bitartrate per tablet or per 5 ml. of syrup. The addict would probably have to inject the narcotic extract from 18—36 tablets to obtain a "high".

In the components of this invention, the tablet (or 5 ml. dose of liquid) should contain about 5 mg. of hydrocodone bitartrate (or equivalent as base or, salt) together with 0.003—0.1 mg. of naloxone hydrochloride (or equivalent as base or, salt) with or without additional drugs such as antihistamines (e.g., chlorpheniramine maleate), vasoconstrictors (e.g., phenylephrine hydrochloride), non-narcotic analgesics (e.g., acetaminophen), antispasmodics, and caffeine. The preferred tablet dose is hydrocodone bitartrate 5 mg. and naloxone hydrochloride 0.03 mg.

Example 3.

Codeine with Naloxone — Codeine phosphate is an effective oral analgesic and antitussive which is generally used in doses of 7.5—60 mg. tablets as an analgesic and 10 mg. tablets or liquid dosages as an antitussive with or without additional non-narcotic drugs like APC (aspirin, phenacetin, and caffeine). The addict would probably have to inject the narcotic extract from 4—8 tablets of the 60 mg. strength to obtain a "high".

In the compositions of this invention, the tablet should contain 7.5—60 mg. of codeine phosphate or (equivalent as base, sulphate or other salt) together with 0.03—1 mg. of naloxone hydrochloride (or equivalent as base or salts), with or without additional drugs such as aspirin, phenacetin, and caffeine. The preferred tablet dosage is codeine phosphate 30 mg. and 0.1 mg. of naloxone hydrochloride, together with aspirin 224 mg., phenacetin 160 mg., and caffeine 32 mg.

Example 4.

Propoxyphene with Naloxone — Propoxyphene hydrochloride is widely-used as an oral analgesic, generally in a 65 mg. dose with aspirin, or with aspirin, phenacetin, and caffeine. The addict would probably have to inject the narcotic extract from 4—8 tablets to obtain a "high".

In the compositions of this invention, the tablet should contain 30—65 mg. of propoxyphene hydrochloride (or equivalent as base or salt) together with 0.03—1 mg. of naloxone hydrochloride (or equivalent as base or salt), with or without aspirin or APC (aspirin, phenacetin, and caffeine). The preferred tablet dosage is propoxyphene hydrochloride 65 mg. and naloxone hydrochloride 0.2 mg., together with aspirin 224 mg., phenacetin 160 mg., and caffeine 32 mg.

Example 5.

Pentazocine with Naloxone — Pentazocine is an effective oral analgesic which is generally used as a tablet containing pentazocine hydrochloride equivalent to 50 mg of the base. The addict would probably have to inject the extract from 4—8 tablets to obtain a "high".

In the compositions of this invention, the tablet should contain 50 mg. of pentazocine base in the form of the hydrochloride (or equivalent as the base itself or other salts)

together with 0.02—0.6 mg. of naloxone hydrochloride (or equivalent as the base or salt). The preferred tablet dose is pentazocine hydrochloride equal to 50 mg. of the base together with 0.2 mg. of naloxone hydrochloride.

The other antagonists mentioned hereinabove, except for the mixed narcotic-antagonist pentazocine, can be substituted for naloxone in the above Examples, at the following multiples or fractions of the naloxene dosages given: N - cyclopropylmethyl - 7,8 - dihydro - 14 - hydroxynormorphinone - 1/3 (of naloxone dosage in mg.) and 21 - cyclopropyl - 7α - (1 - hydroxy - 1 - methylethyl) - 6,14 - *endo* - ethanotetrahydrooripavine - 1/3. N - cyclopropylmethyl - 7,8-dihydro - 14 - hydroxynormorphinone and 21 - cyclopropyl - 7α - (1 - hydroxy - 1-methylethyl) - 6,14 - *endo* - ethanotetrahydrooripavine are also used in combination with pentazocine, each antagonist being at 1/3 the naloxone mg. dosage. It is understood that pharmaceutically acceptable acid addition salts of the narcotic antagonist bases can also be used.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition suitable for oral administration comprising (a) a compound having substantial narcotic activity both orally and by injection the compound being oxycodone, hydrocodone, codeine, propoxyphene or pentazocine or a pharmaceutically acceptable salt thereof, and (b) a narcotic antagonist which is substantially less active orally than by injection, the narcotic antagonist being (1) naloxone or a pharmaceutically acceptable salt thereof, (2) N - cyclopropylmethyl - 7,8 - dihydro - 14 - hydroxynormorphinone or a pharmaceutically acceptable salt thereof, or (3) 21 - cyclopropyl - 7β-(1 - hydroxy - 1 - methylethyl) - 6,14 - *endo*-ethanotetrahydrooripavine or a pharmaceutically acceptable salt thereof, the weight ratio of (a) to (b), calculated as the free base, being

a	Ratio with (b) (1)	Ratio with (b) (2) or (3)
oxycodone	5:0.1	15:0.1
hydrocodone	5:0.03	5:0.01
codeine	30:0.1	90:0.1
propoxyphene	65:0.2	195:0.2
pentazocine	50:0.2	150:0.2

so that (b) does not block the narcotic effect of (a) when the composition is administered orally but does prevent an acute euphoriant effect by (a) when the composition is injected.

2. A composition according to claim 1 wherein (b) is (2) or (3).

3. A composition according to claim 1 substantially as described in any one of the Examples.

J. A. KEMP AND CO.,
Chartered Patent Agents,
14, South Square,
Gray's Inn,
London, WC1R 5EU.

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